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THE COUNCIL FOR TOBACCO RESEARCH–U.S.A., INC.
110 EAST 59TH STREET
NEW YORK, N. Y. 10022
(212) 421-8885

FEB 4 1974

Application for Research Grant

(Use extra pages as needed)

Date: 1/25/74

1. Principal Investigator (give title and degrees):

Stephen M. Ayres, M.D.
Physician-in-Chief

2. Institution & address:

The St. Vincent Hospital
25 Winthrop Street
Worcester, Massachusetts 01610

3. Department(s) where research will be done or collaboration provided:

Medicine

4. Short title of study:

Relative Importance of Cigarette Smoking and Exposure to High Level Automotive Emissions to the Development of Chronic Bronchitis

5. Proposed starting date: July 1, 1974

6. Estimated time to complete: Five Years

7. Brief description of specific research aims:

The specific aim of this study is to determine the relationships among cigarette smokers, exposure to automotive emissions and the development of chronic bronchitis. In addition, we plan to evaluate the frequency of physiologic abnormalities and symptoms in chronic bronchitis and to study the sequential development of chronic obstructive lung disease over an extended time period.

8. Brief statement of working hypothesis:

Chronic bronchitis develops from the interaction of nature and nurture. A variety of inhaled materials, cigarette smoke and automobile exhaust, for example, may lead to small airway disease in genetically susceptible individuals. Small airway disease may or may not progress to symptomatic emphysema depending on the intensity of genetic and enviromental factors.

9. Details of experimental design and procedures (append extra pages as necessary)

The appended reprint details a study of over 450 tunnel and bridge officers conducted over the past three years under contract from the Triborough Bridge and Tunnel Authority. This population group is composed of men who collect tolls and control traffic for seven bridges and two tunnels in New York City. These men are exposed to extremely high concentrations of automotive emissions and have relatively high levels of carboxyhemoglobin. We have shown that more than 75% of the group have laboratory evidence of small airway disease. A Venn diagram (see Figure 1) emphasizes the frequency of abnormal closing volumes and midexpiratory flow rates as well as the frequency of symptoms. While detailed smoking histories have not yet been evaluated, a similar incidence of bronchitis and decreased pulmonary function was observed in both smokers and non-smokers, leading us to question the belief that cigarette smoking is the major cause of small airway disease.

We are requesting support from the Council for Tobacco Research in order to specifically study the interrelationship between genetic abnormality and environmental exposure. The overall study will continue for another three years under contract with the Triborough Bridge and Tunnel Authority, but by virtue of an agreement with union and management, we are committed to study the incidence of coronary artery disease using treadmill and on-site electrocardiographic monitoring techniques.

Since considerable data on the prevalence of bronchitis has been already obtained, we are most anxious to continue the study of pulmonary disease in this group over a relatively long period of time.

We propose to further analyze the population by measuring the alpha I antitrypsin phenotype and by obtaining a detailed family history relating to the possible inheritance of pulmonary disease.(1) Aryl hydrocarbon hydroxylase inducibility will be measured by the technique of Kellerman et al,(2) since these workers have recently shown an increase in the incidence of bronchogenic carcinoma in individuals with higher levels of inducibility suggesting a genetic predisposition.(3) Complete

9. Details of experimental design and procedures (cont'd)

hematologic evaluation, immunelectrophoretic measurement of serum globulins and plasma complement, carboxyhemoglobin and blood lead measurements will be made as part of the overall study.

A population of over 400 men first studied in 1970 will be considered the experimental group. There is relatively little turnover in this group of workers and it is likely that the entire population can be followed for at least five additional years. We will make annual measurements of closing volume, mid-expiratory flow rate, airway resistance and functional residual capacity. These methods are detailed in the accompanying reprint. In addition, the British Research Council Respiratory Symptom Questionnaire and a postero-anterior and lateral chest x-ray will be repeated each year. This data will be stored in an in-house magnetic tape data system and be evaluated each year.

The following specific questions are part of the experimental design:

1. Are carcinoma of the lung, bronchitis or emphysema more common in tunnel workers than the general population?

2. Is there a dose effect between the development of respiratory disease and cigarette smoking in this population?

3. What is the relative importance of exposure to automotive pollution and cigarette smoking in the development of carcinoma of the lung, bronchitis and emphysema?

4. Is it possible to identify genetic markers which predict the development of respiratory disease in a heavily exposed population?

References

1. Lieberman, J., Mittman, C., and Schneider, A.S.: Screening for homozygous and heterozygous alpha$_1$-antitrypsin deficiency. Journal of the American Medical Association, 210, 1969.

2. Kellermann, Gottfried, Shaw, Charles R., Luyten-Kellerman, Mieke: Aryl hydrocarbon hydroxylase inducibility and bronchogenic carcinoma. New England Journal of Medicine, Vol. 289, No. 18, November 1973.

3. Kellermann, G., Luyten-Kellermann, M., Shaw, C.R.: Genetic variation of aryl hydrocarbon hydroxylase in human lymphocytes. American Journal Human Genetics, Vol. 25, 1973.

10. Space and facilities available (when elsewhere than item 2 indicates, state location):

Computer facilities
Chemistry laboratory
St. Vincent Hospital
25 Winthrop Street
Worcester, Massachusetts

Pulmonary Function Laboratory
117 West 12th Street
New York, New York

11. Additional facilities required:

None

12. Biographical sketches of investigator(s) and other professional personnel (append):

Please see attached list.

13. Publications: (five most recent and pertinent of investigator(s); append list, and provide reprints if available).

Please see attached list.

14. First year budget:

A. Salaries (give names or state "to be recruited") Professional (give % time of investigator(s) even if no salary requested)	% time	Amount
Ayres, Stephen M.	10%	0
Technical		
Lab Technician	100%	$9,000 + $540
Computer Technician and Data Analyzer	100%	$10,000 + $600
	Sub-Total for A	$19,000 + $1,140 = $20,140
B. Consumable supplies (by major categories)		
Glassware, gases, chemicals	$3,500	
Questionnaire	$ 500	
	Sub-Total for B	$4,000
C. Other expenses (itemize)		
Reprints and publishing	$ 500	
Computer	$1,000	
Travel	$ 500	
	Sub-Total for C	$2,000
	Running Total of A + B + C	$26,140
D. Permanent equipment (itemize)		
	Sub-Total for D	$26,140
E. Indirect costs (15% of A+B+C)	E	$ 3,921
	Total request	$30,061

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15. Estimated future requirements:

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	$21,147	$4,200	$2,000	0	$4,102	$31,444
Year 3	$22,207	$4,400	$2,200	0	$4,321	$33,128

16. Other sources of financial support:
List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Health Surveillance	Triborough Bridge and Tunnel Authority	$70,000 per year	1/24/72-1/24/76

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Stephen M. Ayres, M.D.

Signature Stephen M Ayres Date 1-30-74

Telephone 617 (Area Code) 798-6177 (Number) (Extension)

Checks payable to

St. Vincent Hospital

Mailing address for checks

25 Winthrop Street

Worcester, Massachusetts 01610

Responsible officer of institution

Typed Name Miss Helen Marie Smith

Title Executive Director

Signature Helen Marie Smith Date 1/30/74

Telephone 617 (Area Code) 798-6066 (Number) (Extension)

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13. Publications:

1. Ayres, Stephen M., Mueller, Hiltrud S., Gregory, John J., Giannelli, Stanley, Jr., and Penny, John L.: Systemic and myocardial hemodynamic responses to relatively small concentrations of carboxyhemoglobin (COHB). Archives of Environmental Health, Vol. 18, April 1969.

2. Ayres, Stephen M., and Buehler, Meta E.: The effects of urban air pollution of health. Clinical Pharmacology and Therapeutics, Vol. 11, No. 3, May-June 1970.

3. Ayres, Stephen M., Giannelli, Stanley, Jr. and Mueller, Hiltrud: Myocardial and systemic responses to carboxy-hemoglobin. Annals of The New York Academy of Sciences, Vol. 174, Article 1, October 1970.

4. Ayres, Stephen M., Giannelli, Stanley, Jr., and Mueller, Hiltrud: Carboxyhemoglobin and the access to Oxygen. An example of human counterevolution. Archives of Environmental Health, Vol. 26, January 1973.

5. Ayres, Stephen M., Evans, Robert, Licht, David, Griesbach, Jane, Reimold, Felicity, Ferrand, Edward F. and Criscitiello, Antoinette: Health effects of exposure to high concentrations of automotive emissions. Studies in bridge and tunnel workers in New York City. Archives of Environmental Health, Vol. 27, September 1973.

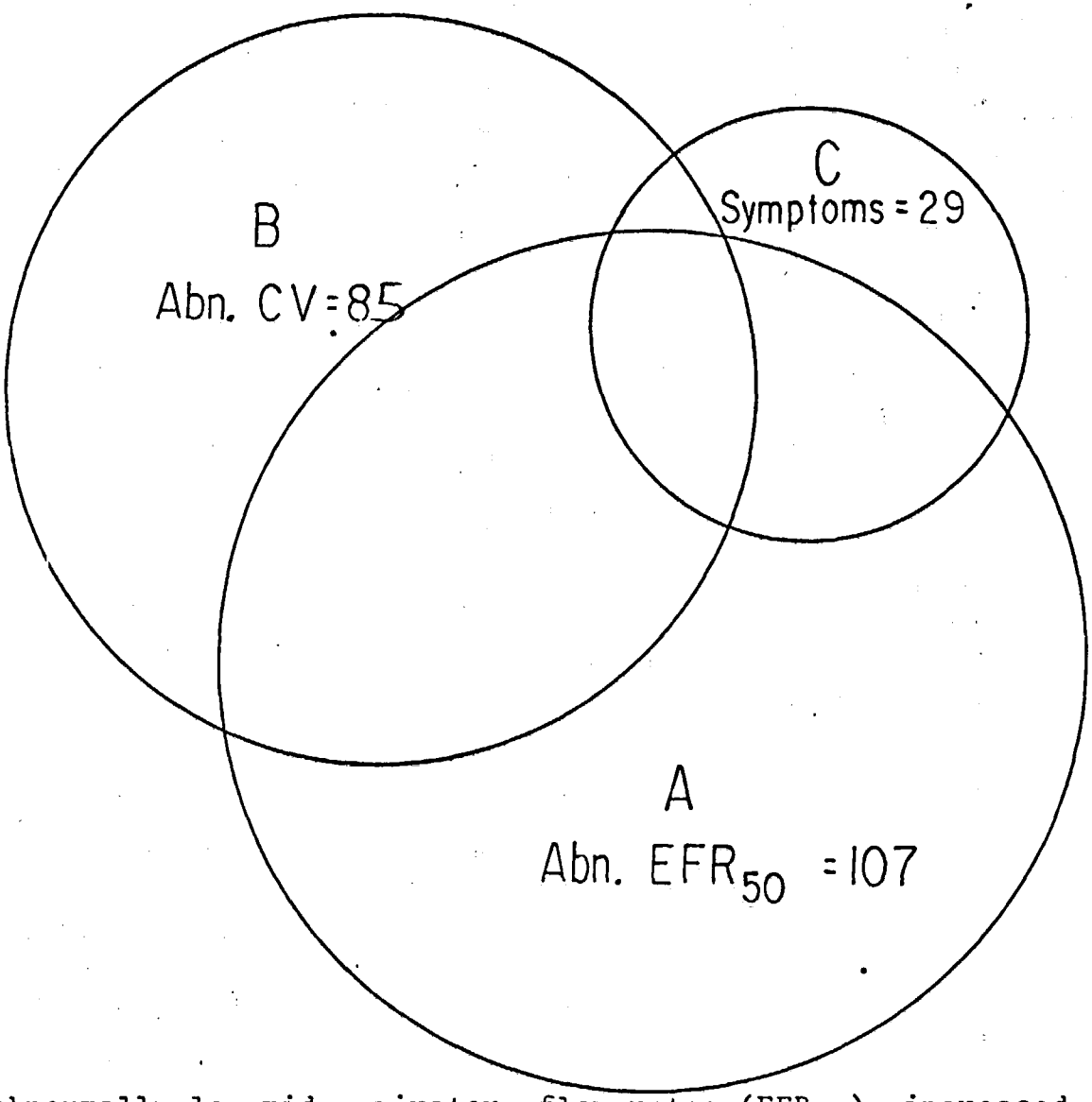

Figure 1 - Distribution of abnormally low mid-expiratory flow rates (EFR_{50}), increased closing volumes (CV) and symptoms of chronic bronchitis in a population of 111 non-smoking bridge and tunnel workers.